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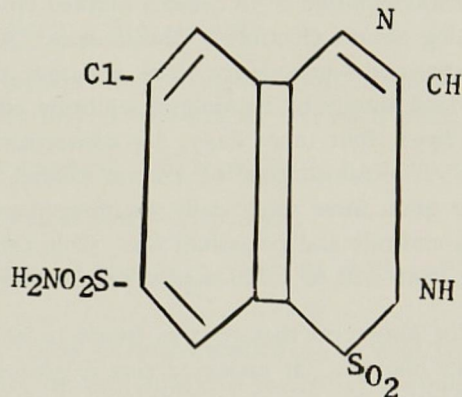
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CHLOROTHIAZIDE (DIURIL) — A NEW NON-MERCURIAL ORAL DIURETIC

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Clinical observation concerning a new non-mercurial oral diuretic designated by the generic name — chlorothiazide¹ constitutes this report. It is designated chemically as 6 - chloro, 7- sulfamyl, 1, 2, 4 - benzothiadiazine - 1, 1-dioxide.



It is not primarily a carbonic anhydrase inhibitor⁴ but seems to possess the factor of exerting considerable influence on the renal tubular transport of electrolytes, causing a marked decrease in the reabsorption of sodium and chloride, and to a lesser degree potassium and bicarbonate.^{2,3,4} The loss of sodium is apparently equal mole for mole to that of chloride.² In large doses it is reported² that bicarbonate is lost in "appreciable" amounts though never to the point of metabolic acidosis as is the case with carbonic anhydrase inhibitors. Smaller but effective diuretic doses produce only relatively minor loss of bicarbonate.

The drug is rapidly and well absorbed by the oral route with onset of action within two hours and a duration of action of somewhat less than 12 hours.^{2,4} The pattern of electrolyte excretion with its marked chloruretic effect and rapid onset suggested a similarity to mercurial diuretics, and further that pretreatment with ammonium chloride might enhance its effect and protect the patient from hypochloremic alkalosis.

Chlorothiazide was employed in several different groups of patients. All were kept on one gram sodium chloride diets and all but two were fully digitalized. All other diuretic agents were stopped except for ammonium chloride. There was a total of 39 patients in the study, all in congestive failure at the time of drug administration.

GROUP I: Patients seen for the first time in congestive failure in whom chlorothiazide was administered in lieu of a mercurial diuretic.

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GROUP II: Patients in chronic congestive heart failure who required only sporadic mercurial injections or were taking regular oral mercurial or non-mercurial diuretics.

GROUP III: Patients in chronic congestive heart failure who required regular mercurial injections.

GROUP IV: Patients in refractory state of congestive heart failure in whom regular mercurials did not produce satisfactory diuresis.

Since chlorothiazide was reported^{2,3,4} to cause a marked chloruresis, several patients were followed by checking serum electrolyte disturbances. As the study progressed, routine determinations appeared unnecessary since apparent protection against hypochloremia could be provided simply by ammonium chloride administration. The latter was given in one gram doses, four times daily, 3-4 consecutive days a week, as with the mercurial diuretics. The substitution of enteric coated potassium chloride for ammonium chloride, one gram three times daily for three days, may more completely protect the patients from chloride and potassium loss. Chlorothiazide was administered in divided doses ranging from 250 to 1,500 mgms. per 24 hours, 3-7 days a week.

The average dose for long-term therapy was found to be 250 mgms. three times daily at roughly six hour intervals. It appeared that a greater diuretic response was obtained by giving chlorothiazide on a divided dosage schedule, 2-3 times a day than by a single large dose in the morning, and over 3-4 consecutive days each week.

Individual dosage adjustment was, of course, necessary since all patients did not respond in a similar manner, some requiring as much as 1,500 mgms. per day, and others as little as 250 mgms. one day a week. The usual initial dose was 250 mgms. t.i.d., 3-4 consecutive days a week and ammonium chloride 4-6 grams per day the remaining days of the week. Larger doses gave no greater diuresis than smaller effective doses. Subsequent dosage was determined by diuretic response and further need of therapy. There was no evidence of loss of effectiveness of chlorothiazide in the presence of ammonium chloride acidosis, as has been claimed by Maren⁵ to be the case with the carbonic anhydrase inhibitor, acetazolamide.

The onset of diuresis was more gradual than with a parenteral mercurial, but continued in a more sustained and less vigorous manner, so that practically all patients agreed it did not cause them the same degree of muscular discomfort and marked frequency of urination with the consequent frequent loss of sleep seen with the shorter and more violent action of a parenteral mercurial.

RESULTS OF STUDY

GROUP I: Patients seen for the first time in congestive failure in whom chlorothiazide was administered in lieu of a mercurial diuretic.

6 cases: 3 arteriosclerotic heart disease — 2 hypertensive cardiovascular disease — and 1 rheumatic heart disease.

Average dosage — 250 mgms. t.i.d. for 3 days.

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Average weight loss — 6 pounds at the end of a 3 day period.

GROUP II: Patients in chronic congestive heart failure who required only occasional mercurial injections; or were taking oral mercurial or non-mercurial diuretics.

10 cases: 6 arteriosclerotic heart disease — 3 hypertensive cardiovascular disease — and 10 rheumatic heart disease.

Duration of time followed — 6 weeks to 4 months.

Average time — 2½ months.

Average dosage — 250 mgms. t.i.d. 3 consecutive days each week to 500 mgms. t.i.d. 3 consecutive days each week.

One case received as little as 125-250 mgms. one day a week.

Average weight loss — 5 pounds.

Usual loss — 3 pounds to 8 pounds at the end of each course.

COMMENT: No case failed to be controlled as well as with mercurials (oral and parenteral) or with oral non-mercurial combinations with mercurials.

3 cases much improved over mercurial program.

2 cases receiving regular non-mercurial oral diuretics and occasional mercaptomerin promptly lost 5-8 pounds when placed on chlorothiazide.

1 case on an oral mercurial lost 5 pounds in 4 days after use of chlorothiazide.

GROUP III: Patients in chronic congestive heart failure who required regular mercurial injections.

10 cases: 4 arteriosclerotic heart disease — 1 hypertensive cardiovascular disease — and 5 rheumatic heart disease.

Time followed — 8 to 20 weeks.

Average dosage — 250 mgms. t.i.d. 3 consecutive days each week, to 500 mgms. b.d. or t.i.d.

Prior diuretic — Mercaptomerin or combinations of with chlormerodrin or non-mercurial oral diuretics. Average frequency of parenteral mercury was every 7 to 14 days.

After chlorothiazide — average weight loss — 6 pounds; one case — 12 pounds less.

COMMENT: No case a failure. Every case as well controlled and a great deal more smoothly than on previous diuretic schedule.

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GROUP IV: Patients in refractory state of congestive failure in whom regular mercurials did not produce satisfactory results.

3 cases: all arteriosclerotic heart disease.

All were unimproved on mercurial program.

All were unimproved on chlorothiazide.

1 case unimproved then did better when returned to mercurials.

TYPICAL CASE REPORTS

GROUP I: N.G. — 50 year old male was admitted to the Henry Ford Hospital in congestive failure from arteriosclerotic and hypertensive heart disease. He had been on digitoxin 0.2 mgms. q.d. and on a low salt diet. After admission with no change in therapy, his weight remained stable for three days. On the morning of the fourth day, he was begun on 500 mgms. chlorothiazide, b.i.d. At the end of two days he had lost 7 pounds in weight and all signs of congestive heart failure had cleared except for questionable minimal hepatic enlargement. He was continued on chlorothiazide for three more days with the further loss of one pound in weight. Serum sodium, potassium, chloride and carbon dioxide were drawn at this time and all were within normal limits. He was then given 2 cc. of parenteral mercurial to see if any further diuresis could be obtained. There was no change in weight or physical findings.

He was discharged to the Out-Patient Department on maintenance digitoxin and a one gram salt diet, and followed at about monthly intervals requiring parenteral mercurials. After three months he again was given chlorothiazide, 250 mgms. t.i.d., three days a week, and ammonium chloride, 1 gram q.i.d. the other four days of the week. Within 48 hours of institution of chlorothiazide therapy, he lost four pounds in weight and his failure cleared. He has remained out of failure on this program for three months and has required no subsequent mercurials.

GROUP II: B.Z. — 44 year old female with rheumatic heart disease, auricular fibrillation and chronic congestive failure. She had been on digitoxin, ammonium chloride, one gram salt diet, chlormerodrin five days a week and occasionally required a parenteral mercurial. She was begun on chlorothiazide, 250 mgms. t.i.d., three days a week with 4 grams ammonium chloride the other four days of the week. On this program she lost 5 pounds in weight within four days with relief of symptoms and has maintained her improvement for over two months with no need for chlormerodrin or any parenteral mercurial.

GROUP III: H.G. — 70 year old female has been followed at the Henry Ford Hospital for many years with hypertensive cardiovascular disease, auricular fibrillation and chronic congestive failure. She had been on gitalin 0.5 mgms. q.d., one gram salt diet, raudixin, 100 mgms. b.i.d. and for many months had required parenteral mercurials every 7-10 days with intermittent ammonium chloride. Even on this program she had periodic congestive failure with orthopnea and paroxysmal nocturnal dyspnea and edema, usually beginning a few days prior to each mercurial injection. She was begun on chlorothiazide, 250 mgms. t.i.d., 3 days a week and ammonium chloride the other four days of the week.

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On this program, she has not needed any mercurial diuretic for five months, and has had no orthopnea, paroxysmal nocturnal dyspnea or edema for the first time in 2-3 years.

GROUP IV: H.F. — 65 year old male with chronic, severe, intractable congestive failure and auricular fibrillation on an arteriosclerotic basis. He has been on digoxin 0.625 mgms. q.d., one gram salt diet, intermittent ammonium chloride and parenteral mercurials, and in the past on chlormerodrin and acetazolamide therapy. He had not been well controlled on any of these programs. Recently he had become almost completely resistant to even parenteral mercurials. He was begun on 500 mgms. chlorothiazide b.i.d., 3 days a week with intermittent ammonium chloride without response. Dosage was increased finally to 500 mgms. t.i.d. every day but still with no satisfactory response. To this program was added parenteral mercurials, 2 cc. every 3-7 days, but with only minimal improvement — that is, a weight loss of from 3-4 pounds with each injection. However, he would regain this weight within 24 to 72 hours. In summary, it was felt that chlorothiazide was of no significant benefit to this patient.

TOXICITY:

Studies to date indicate chlorothiazide has little or no toxicity, however, as with all new drugs, alertness for signs of toxicity must be maintained. Its greatest potential danger seems to be the possibility of producing hypochloremia, hypokalemia or low sodium syndromes, exactly as with mercurials.

Patients with kidney disease should be watched closely and possibly also those with liver function impairment. The drug is apparently primarily excreted by the kidney, being eliminated completely within 24 to 48 hours.^{2,4} However, in nephrectomized dogs given chlorothiazide, considerable quantities could be recovered from the biliary tract.²

Nausea or vomiting did not occur in any of our patients, the drug being exceedingly well tolerated. No neurologic symptoms such as headache, paresthesias, peripheral neuritis, etc. were found. Skin eruptions were not encountered; hemorrhagic and renal disturbances were checked for, but not present, and are reported absent.^{2,4} In short, no evidence of toxicity was uncovered in any of the patients treated in this series.

COMMENTS:

Chlorothiazide appears to represent a significant advance in the diuretic management of congestive heart failure, approaching the effectiveness of parenterally administered mercurials, its decided advantages being:

- 1). Effective oral administration.
- 2). Apparent lack of toxicity.
- 3). Lesser potassium and bicarbonate loss than with carbonic anhydrase inhibitors, and therefore not as likely to produce metabolic acidosis or hypokalemia.

- 4). Sustained diuretic action over prolonged periods (months) without apparent development of tolerance to the drug and without necessity of increasing dosage, and therefore, more even control of failure than seen with intermittent parenterally administered mercurials.
- 5). Fairly rapid onset and peak of action.

It should be stated as advisable to respect the potential danger of the drug as with mercurials, in giving it to patients who are salt depleted, and to be cautious in using it without the replacement of chlorides by means of ammonium chloride where the latter can be safely administered.

Study is being given to the possibility of allowing less stringent dietary sodium chloride restriction in patients with congestive failure while being given chlorothiazide, since its rapid saluretic action may prevent the accumulation of fluid.

SUMMARY AND CONCLUSIONS:

Chlorothiazide (6-chloro-7-sulfamyl-1,2,4-benzothiazidiazide -1, 1-dioxide) was found to be an extremely effective oral non-mercurial diuretic agent resembling most closely pharmacologically, the mercurial diuretics, particularly in regard to the elimination of sodium and chloride and to a lesser increase, the excretion of potassium and bicarbonate.

Therapeutic dosage varied from 250 to 1,500 mgms. per day with apparent increased effectiveness on a divided dosage schedule. Usual maintenance dose was 500 to 1,000 mgms. three to four consecutive days of the week, alternating with ammonium chloride for its possible potentiating and antihypochloremic effect.

Its effectiveness was not diminished with constant administration, even over a period of several months. Chlorothiazide was found to be an effective replacement for regular oral or parenteral mercurial therapy, and resulted in a smoother control of failure than that seen with intermittent parenteral mercurials in the majority of cases.

Effective for short term diuretic action also (1 to 3 days).

In our limited experience it was of no value in intractable, mercurial resistant cases.

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